REMARKS

Status of Claims

Claims 1, 3, 9-12 and 14-28 are pending. Claims 1, 3, and 9-12 have been rejected. Claims 1 and 9 have been amended. Support for the amended claims can be found throughout the specification, in paragraphs 0023, 0024, 0025 and paragraph 0034 of the Application as filed.

Claim 7 has been canceled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

Applicants respectfully assert that the amendments to the claims add no new matter.

EXAMINER INTERVIEW

Applicants note that Applicants' representatives Prakash Subbiah and Mauricio Alvarez spoke with Examiner Martin over phone. Applicants thank the Examiner for his courtesy during the telephonic interview. Applicants discussed the outstanding issues to advance the prosecution. Specifically, Applicants noted that CD3 is not disclosed or taught in the cited references. The Examiner noted that he would reconsider his position based on claim amendments. The Examiner further noted that he would consider removing the rejections after receiving this Response.

Claim objections

Claims 6, 7, 8 and 13 have been objected to allegedly because the text of cancelled claims should be deleted from the claims listing.

In response, Applicants note that the text of cancelled claims has been deleted. Therefore, Applicants request withdrawal of the claim objections.

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1, 3 and 6, 7, 9-13 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Fontenot et al. (*The Journal of Clinical Investigation*. 112(5). 2003). ("Fontenot") in view of Shapiro (2003).

The Examiner asserts that Fontenot allegedly teaches a method wherein peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) cells from subjects diagnosed with chronic beryllium disease (CBD) are stained with monoclonal antibodies to CD4, CD8 and CD28 in order to identify the lymphocyte (T-cell) population and contacting the identified BAL T-cell subpopulation with the intracellular protein strain CFSE. The Examiner further asserts that Shapiro teaches a viability marker such as TO-PRO3. As such the Examiner alleged that it would have been obvious to modify the method of Fontenot for monitoring the cellular proliferation of a cell marker selected subpopulation (CD4 PBL cells) using CFSE to include a viability marker to exclude the dead cells from the assay.

Applicants respectfully disagree. In response, Applicants note that claims have been amended to recite the use of a viability marker in combination with an intracellular protein stain for a cell proliferation marker and a cell surface marker to allow for the selection of a subpopulation of a peripheral blood leukocyte population, wherein said surface marker is CD3. To that effect, Applicants further add that neither Fontenot, nor Shapiro, teach or suggest using a cell surface marker CD3 to allow for the selection of a subpopulation of cells. Further, the failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103.

Further, it would not have been obvious for a skilled artisan to arrive at the present invention for the artisan would not have readily predicted success by combining these elements, and certainly neither Fontenot nor Shapiro, alone or when combined, provide all of the elements of the claimed invention in a manner that would allow an artisan to predict success as the invention demonstrates. Moreover, whether or not the references can be combined or modified as alleged by the Examiner does not render the resultant combination obvious (see MPEP 2143.01).

Moreover, Fontenot describes how the function of the BAL cells was impaired by decreased CD28. Indeed Fontenot states that:

> Here, we examined the role of CD28-mediated costimulation in antigen-specific T cell activation and survival. The results demonstrate an apparent evolution of independence from CD28-mediated costimulation that correlates with memory cell differentiation. Memory CD4+ T cells in blood continued to require CD28 costimulation for proliferative and cytokine responses to beryllium. In the lung, proliferation and secretion of Th1-type cytokines by effector memory cells were functionally independent of CD28 costimulation, and a proportion of these cells stopped expressing CD28. These CD4+CD28− T cells showed decreased proliferative capacity and an increased rate of apoptosis after stimulation with antigen, suggesting transition to a presenescent state.

(See, Fontenot p. 777, top-left paragraph). Hence, Fontenot does not describe nor suggest a predictive response of PBMC to beryllium salt (as measured by CFSE) as a disease indicator, as the present invention demonstrates (see paragraphs 0096-0099).

Further, use of CD3 as a cell surface marker in the invention carries an unexpected advantage in that it serves as a reliable marker. In comparison, Fontenot does not disclose the reliable use of CD4, given that Fontenot solely measures surface expression of CD4 and this can be problematic since CD4 can be downregulated once the cells are activated (see paragraph 0085 of the application as filed). Thus, measuring surface CD4 cell alone, as Fontenot discloses, does not provide for a reliable and efficient method of measuring beryllium sensitivity in an individual. Unlike Fontenot, the present invention compensates for this by also measuring intracellular CD4 levels (see last paragraph of specification as filed, bottom of page 25) and this is a process that Fontenot does not disclose and hence it is unexpected over the teaching of Fontenot. Therefore, the present invention discloses various unexpected advantages over Fontenot in that measuring CD3 cell surface marker and intracellular CD4 levels provide for a reliable, reproducible and efficient measurement of beryllium sensitivity in individuals.

In summary, Fontenot does NOT use a cell proliferation marker, or a viability marker, or a cell surface CD3 marker, to measure the proliferation of CD3+ /$CD4^+$ peripheral T cells,

and Shapiro does not remedy this deficiency. Thus, a skilled artisan would not find the present invention to be obvious in view the Fontenot alone, nor when combined with Shapiro. Applicants therefore request withdrawal of the claim rejections.

Conclusion

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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